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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,815	04/30/2001	Gary E. Rehm	MSE #2610	3326

7590 04/05/2004

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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 04/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/844,815	REHM ET AL.	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-16* is/are pending in the application.

4a) Of the above claim(s) *11-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,10,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10.31.03 01.21.04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

The Request for Continued Examination filed December 22, 2003 is acknowledged and has been entered.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-7, 9, 10, 15 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, part (b) the recitation "correlating the concentration of trypsin inhibitor with the detectable response from the cleaving of the substrate" is vague and indefinite. It is unclear if a concentration of trypsin inhibitor has been determined and then correlated to a detectable signal or if the detectable signal is detected and this detection is then used to determine the concentration of trypsin inhibitor.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-4, 7, 9, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uenoyama et al (US 5,856,117) in view of Ausubel (Current

Protocols in Molecular biology. Passage Text, Current Protocols in Molecular biology, New York, Wiley & Sons, US, vol. 3, 1995, page A03F12) and further in view of Berry et al (US 5,384,247).

Uenoyama et al disclose a method for measuring the concentration of urinary trypsin inhibitors which involves mixing a urine sample, trypsin, and a buffer solution and the addition of a substrate solution to cause the enzyme reaction, and measuring the activity of trypsin (col 5, lines 39-60). Uenoyama et al also teach the use of dimethylfomamide as the solvent (col 6, line 11) and a buffered pH of 7.8 (col 7, line 46) and the substrate present in a concentration of 1 to 50 mmol/l (col 4, line 16) and trypsin in the concentration of 10 to 500 mg/l preferably 20 to 100 mg/l (col 5, line 52). Uenoyama et al also disclose that the buffer solution can be a Tris buffer or phosphate buffer (col 6, lines 46-48).

The method of Uenoyama et al differs from the instant invention in failing to disclose the use of a polycarboxylic chelating agent. Uenoyama et al also fails to teach reference to a control sample lacking the polycarboxylic chelating agent.

Ausubel teaches the use of a polycarboxylic chelating agent solution with a sample. Ausubel teaches the polycarboxylic chelating agent can be EDTA. Ausubel teaches that EDTA is added as a chelating agent to bind calcium and magnesium ions that can interfere with the action of trypsin.

Berry et al (US Patent 5,384,247) teach the use of EGTA and EDTA as chelating agents which inhibit the interfering ions of calcium in a urine sample (col 4, line 53 - col 6, line 17) (claims 27 and 34). Berry et al also teaches the use of a control

sample lacking the polycarboxylic chelating agent (col 16). Berry et al teaches that the reagent can be impregnated on an appropriate carrier and that it can be in dry form. The use of these chelating agents reduce the free concentration of interfering ions to levels where interference is no longer significant and increase the sensitivity of the enzyme to an analyte with respect to the interfering ion (col. 3, lines 45-52).

It would have been obvious to one of ordinary skill in the art to incorporate the use of polycarboxylic chelating agents as taught by Ausubel into the method of Uenoyama et al because Uenoyama et al teaches offsetting the effects of calcium in a sample and Ausubel teaches that EDTA/trypsin solutions are used together to offset the effects of calcium that can interfere with the action of trypsin. Further, Ausubel teaches that EDTA does not inhibit trypsin activity.

It also would have been obvious to one of ordinary skill in the art to incorporate the polycarboxylic chelating agents of Berry et al and the use of a control lacking the polycarboxylic chelating agent into the modified method of Uenoyama et al because Berry et al shows that the use of these chelating agents provide the advantage of reducing the free concentration of interfering ions to levels where interference is no longer significant and also increase the sensitivity of the enzyme to an analyte.

With respect to the specific concentration of the chelating agents recited in the instant claims, the optimum concentration of chelating agent can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art.

5. Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uenoyama et al (US 5,856,117) in view of Ausubel and Berry et al as applied to claims 1-4, 7, 9 15 and 16 above, and further in view of May et al (GB 2,204,398).

See above for teachings of Uenoyama et al, Ausubel and Berry et al.

Uenoyama et al, Ausubel, and Berry et al differ from the instant invention in failing to disclose dry test reagents and a dry test device which the urine test sample can flow by dipping the dry test device into the buffered assay medium.

May et al disclose a device comprising a hollow casing constructed of moisture-impervious solid material containing a dry porous carrier which communicates indirectly with the exterior of the casing, a sample receiving member protrudes from the casing such that a liquid test sample can be applied to the receiving member and permeate to the porous carrier which contains impregnated reagents (page 15, lines 16-35 and page 16, lines 1-9). This diagnostic test device allows for quick and convenient use and requires the user to perform as few actions as possible (page 2, lines 29-35).

It would have been obvious to one of ordinary skill in the art to use the device of May et al to practice the method of Uenoyama et al as modified by Ausubel and Berry et al, because May et al shows that the device allows for quick and convenient use and requires the user to perform as few actions as possible, where all the necessary reagents are all present on a single solid support.

6. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uenoyama et al (US 5,856,117) in view of Ausubel and Berry et al as applied to claims 1-4, 7, 9 15 and 16 above, and further in view of Nanbu et al (US 6,130,055).

See above for teachings of Uenoyama et al, Ausubel and Berry et al.

Uenoyama et al differ from the instant invention in failing to disclose arginine or lysine derivatives as the substrate for trypsin.

Nanbu et al discloses a method for measuring the concentration or activity of urinary trypsin inhibitor. Nanbu et al teach mixing a sample, trypsin solution, and a substrate in a solution and measuring the tryspin activity. Nanbu et al also teach that this substrate may come from the amino acid residues of the L-type (col 2, lines 13-23). The use of this substrate would allow for excellent solubility.

It would have been obvious to one of ordinary skill in the art to incorporate the trypsin substrates of Nanbu et al into the method of Uenoyama et al as modified by Ausubel and Berry et al because Nanbu et al shows that the use of the L-type amino acid residues allows for excellent solubility (col 2, line 23).

Response to Arguments

7. Applicant's arguments filed December 22, 2003 have been fully considered but they are not persuasive.

Applicant argues (page 7, line 1 remarks section) that the present invention is directed to a method for eliminating the interference of calcium ions with trypsin activity so that the trypsin inhibitor activity in a urine sample can be accurately measured. In response to applicant's argument it is noted that the features upon which applicant relies (i.e., a method for eliminating the interference of calcium ions) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification,

limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant argues that addition of EGTA to a urine sample containing trypsin does not inhibit trypsin activity and that this result is surprising since it is know that most enzyme are sensitive to selective binding agents, such as chelators and that it is well known in the art that the enzyme, alkaline phosphatase, is inhibited by EGTA. Applicant specifically directed Examiner's attention to (Zygowitz, E. 1975 and Shan et all, 1983, Anal. Chem., 65:3053-3060). This is not found persuasive because as shown above Ausubel teaches the use of EDTA in combination with trypsin and that this chelating agent does not inhibit trypsin activity but rather is used to bind ions that can interfere with the action of trypsin.

Applicant argues that Uenoyama et al fails to teach or suggest that the calcium present in the urine should be inactivated and that Uenoyama et al also fails to teach or suggest that addition of a polycarboxylic acid chelator to the urine sample inactivate calcium ions so that they cannot interfere with trypsin. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the calcium present in the urine should be inactivated, and inactivates calcium ions so that they cannot interfere with trypsin) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant argues that Berry et al fails to teach or suggest that polycarboxylic chelators, such as EDTA and EGTA are capable of binding strongly enough to calcium ions to completely prevent the ions from binding to trypsin. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that polycarboxylic chelators, such as EDTA and EGTA are capable of binding strongly enough to calcium ions to completely prevent the ions from binding to trypsin) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant argues that Berry et al limited the discussion of enzymes to transferases and hydrolases, and did not disclose the effect of chelators on any proteases. Examiner agrees that Berry limited the discussion to transferases and hydrolases. However, trypsin's are hydrolase enzymes.

Applicant argues that Berry et al teach that the bound ions are removed from the sample, rather than simply inactivated as in the present invention. This is not found persuasive because nowhere in the claims does it state that the ions are inactivated. Further, there is no limitation in the claim excluding the removal of bound ions from the sample.

Applicant argues that tertiary reference May et al., and Nanbu et al do not cure the deficiencies of the primary and secondary reference and the cited combination of prior art does not render the present invention obvious. This is not found persuasive

because it is the Examiner's position that the combination of Uenoyama et al, Ausubel and Berry et al read on the instantly recited claims and therefore, the combination of the tertiary references with Uenoyama et al, Ausubel and Berry et al is appropriate.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary W. Counts
Examiner
Art Unit 1641
March 24, 2004

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04/01/04